5 Minute JournalClub

Key SABCS Presentations

Issue 7, 2011

The Efficacy of Adjuvant Capecitabine-Containing Regimens in Medium- to High-Risk Breast Cancer

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CME INFORMATION

OVERVIEW OF ACTIVITY

The annual San Antonio Breast Cancer Symposium (SABCS) is unmatched in its significance with regard to the advancement of breast cancer treatment. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year in which published results from a plethora of ongoing clinical trials lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across all breast cancer subtypes. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of the rapidly evolving data sets in breast cancer. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest SABCS meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for breast cancer.

LEARNING OBJECTIVE

- Identify the incremental efficacy and toxicity associated with the addition of capecitabine to the adjuvant management of high-risk early breast cancer.

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Click here for SABCS papers on HER2-negative breast cancer

In 2001 the first results from the ATAC trial demonstrated the superiority of an AI (anastrozole) over tamoxifen. One year later a CALGB study showed an advantage for dose-dense AC→paclitaxel, and not long after that US Oncology proved that TC was better than AC and along the way the NSABP presented data on the Onco*type* DX® assay to help select patients for adjuvant chemo. However, since the presentation of those important yet modest research advances, one could make the argument that not a whole lot else positive has happened in adjuvant treatment for the 80 percent of patients with HER2-negative breast cancer.

2010 didn't do much to change this situation — at least that's my conclusion after watching Alan Coates' San Antonio "Year in Review" presentation on the management of early breast cancer. Of the 18 papers he discussed during this talk, none seem likely to lead to a meaningful change in the mortality of this disease. Perhaps the most provocative of the bunch highlighted by Dr Coates were the three neoadjuvant HER2-positive papers reviewed in a previous issue of this series. However, the HER2-negative papers that were "featured" made me long for a myeloma-like infusion of new agents that actually work.

Unfortunately, it's not totally clear that this is on the horizon, especially if the data sets coming out in San Antonio are any indication. What we saw there were mainly a few legacy studies evaluating adjuvant chemotherapy, including:

1. Findings from another **CALGB trial** suggesting similar outcomes with four and six cycles of dose-dense paclitaxel or AC.

2. **Two trials** testing the addition of capecitabine to anthracycline/taxane regimens demonstrating questionable or no benefit, although **two other** related data sets suggested a slightly greater advantage with cape in triple-negative disease.

3. Early **tolerability data** on "maintenance" capecitabine after an anthracycline and/or a taxane — a strategy that makes sense, but no definitive efficacy data exist yet.

4. Another **early safety report** in a trial evaluating bevacizumab/chemotherapy in the adjuvant setting, but the recent negative results of two adjuvant trials of bev in colon cancer have perhaps dampened enthusiasm for this approach.

It's a real disconnect to walk through the halls of San Antonio and see thousands of investigators presenting a seemingly endless array of data sets and still contemplate the fact that the current overall impact of this effort at a patient care level — especially in the most prevalent HER2-negative breast cancer subset — is relatively modest. It makes one wonder if we will soon see the payoff of this extensive investment in research and whether there is any way to change the trajectory of progress.

Next up on our final San Antonio issue of *5-Minute Journal Club*: Clinical trials in metastatic disease, including studies of combinations of biologic agents

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The Efficacy of Adjuvant Capecitabine-Containing Regimens in Medium- to High-Risk Breast Cancer

Presentations discussed in this issue

O'Shaughnessy J et al. **First efficacy results of a randomized, open-label, phase III study of adjuvant doxorubicin plus cyclophosphamide, followed by docetaxel with or without capecitabine, in high-risk early breast cancer.** San Antonio Breast Cancer Symposium 2010;**Abstract S4-2**.

Joensuu H et al. **FinXX final 5-year analysis: Results of the randomized, open-label, phase III trial in medium-to-high risk early breast cancer.** San Antonio Breast Cancer Symposium 2010;**Abstract S4-1**.

Slides from presentations at SABCS 2010 and transcribed comments from a recent interview with William J Gradishar, MD (1/4/11)

First Efficacy Results of a Randomized, Open-Label, Phase III Study of Adjuvant Doxorubicin Plus Cyclophosphamide, Followed by Docetaxel with or without Capecitabine, in High-Risk Early Breast Cancer[1]

FinXX Final 5-Year Analysis: Results of the Randomised, Open-Label, Phase III Trial in Medium-to-High Risk Early Breast Cancer[2]

[1]O'Shaughnessy J et al.
Proc SABCS 2010;Abstract S4-2.

[2]Joensuu H et al.
Proc SABCS 2010;Abstract S4-1.

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First Efficacy Results of a Randomized, Open-Label, Phase III Study of Adjuvant Doxorubicin Plus Cyclophosphamide, Followed by Docetaxel with or without Capecitabine, in High-Risk Early Breast Cancer

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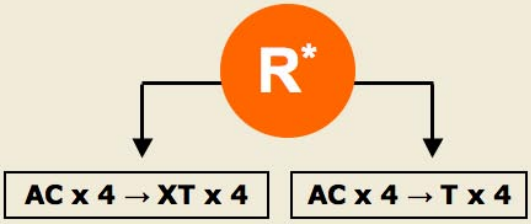
US Oncology 01-062 Study Design

Accrual: 2,611 (Closed)

Eligibility
Aged 18 to 70 years
High-risk, histologically confirmed breast cancer
Node-positive or if node-negative: tumor >2 cm or >1 cm and ER/PR-negative
Surgically resectable disease
No evidence of metastasis



AC = doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2, d1, q3wk

XT = capecitabine 825 mg/m^2 bid, d1-14; docetaxel 75 mg/m^2, d1, q3wk

T = docetaxel 100 mg/m^2, d1, q3wk

Primary endpoint: Disease-free survival

Secondary endpoints: Overall survival and safety

*Patients with HER2-positive disease could receive trastuzumab after ASCO 2005

O'Shaughnessy J et al. *Proc SABCS* 2010;Abstract S4-2.

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Survival and Safety

	AC → XT	AC → T	HR (95% CI); *p*-value
5-year disease-free survival (DFS)	89%	88%	0.84 (0.67-1.05); $p = 0.125$
5-year overall survival (OS)	94%	92%	0.68 (0.51-0.92); $p = 0.011$
Adverse events	99.8%	100%	NR
Serious adverse events	20.2%	15.6%	NR

NR, not reported

O'Shaughnessy J et al. *Proc SABCS* 2010;Abstract S4-2.

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Author Conclusions

- There was no improvement in DFS with AC → XT versus AC → T (89% vs 88%; $p = 0.125$).
- Patients treated with AC → XT had a significantly greater OS (94%) compared to those treated with AC → T (92%) ($p = 0.011$).
  - These results must be interpreted with caution due to the lower than expected event rate at 5 years.
- Exploratory Ki-67 analysis suggested benefit of capecitabine in patients with more highly proliferative cancers (data not shown).
- The incidence of adverse events including serious adverse events was similar between the groups.
- In the AC → XT group, there were higher rates of Grade 3 hand-foot syndrome (18.1% vs 3.8%) and Grade 3 or 4 stomatitis (9.1% vs 4.5%) and diarrhea (5.1% vs 2.9%).
- Grade 3 or 4 febrile neutropenia was higher in the AC → T group (13.1%) vs the AC → XT group (9.4%).

O'Shaughnessy J et al. *Proc SABCS* 2010;Abstract S4-2.

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FinXX Final 5-Year Analysis: Results of the Randomised, Open-Label, Phase III Trial in Medium-to-High Risk Early Breast Cancer

Joensuu H et al.

Proc SABCS 2010;Abstract S4-1.

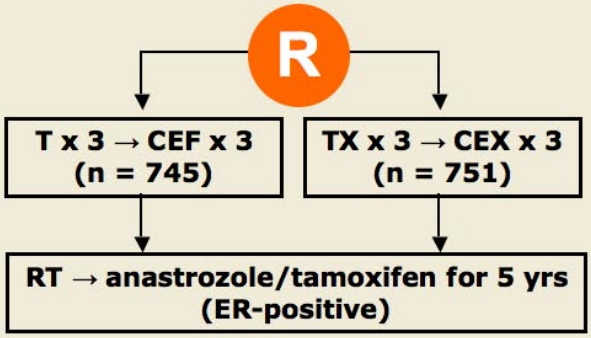
FinXX Phase III Study Design

Eligibility (N = 1,500)

Histologically confirmed invasive node-positive breast cancer or node-negative if tumor > 20 mm and PR-negative

<65 years old

Primary objective:
Recurrence-free survival (RFS) at 5 years



T = docetaxel

CEF = cyclophosphamide, epirubicin, 5-FU

TX = capecitabine, docetaxel

CEX = cyclophosphamide, epirubicin, capecitabine

Joensuu H et al. *Proc SABCS* 2010;Abstract S4-1.

Survival Outcomes (Median Follow-Up 5 Years)

	T/CEF (n = 745)	TX/CEX (n = 751)	HR (95% CI)	*p*-value
Recurrence-free survival				
3-year rate	88.9%	92.4%	0.66 (0.47-0.94)	0.02
5-year rate	84.1%	86.6%	0.79 (0.60-1.04)	0.087
Overall survival				
3-year rate	95.3%	96.1%	—	—
5-year rate	89.7%	92.6%	0.73 (0.52-1.04)	0.080

Joensuu H et al. *Proc SABCS* 2010;Abstract S4-1.

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RFS by Biologic Subtype (Exploratory Analysis)

Biologic Subtype	HR	*p*-value
ER+ and/or PR+, HER2- (n = 1,009)	0.91	0.591
ER+ and/or PR+, HER2+ (n = 163)	1.11	0.845
ER- and PR-, HER2- (n = 202)	**0.48**	**0.0177**
ER- and PR-, HER2+ (n = 122)	0.91	0.786

Joensuu H et al. *Proc SABCS* 2010;Abstract S4-1.

Grade 3/4 Adverse Events

Adverse Event	T/CEF (n = 743)	TX/CEX (n = 751)	*p*-value
Neutropenia	98.1%	86.0%	<0.0001
Hand-foot syndrome	0.3%	11.2%	<0.0001
Infection with neutropenia	12.4%	5.8%	<0.0001
Nail effects	0.5%	4.9%	<0.0001
Febrile neutropenia	8.8%	4.4%	0.0008
Stomatitis	1.6%	4.2%	0.0048
Myalgia	7.8%	1.9%	<0.0001

Joensuu H et al. *Proc SABCS* 2010;Abstract S4-1.

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Author Conclusions

- TX/CEX did not improve RFS or OS significantly compared to T/CEF.
- Exploratory subgroup analyses suggest:
  - TX/CEX is more effective than T/CEF in patients with triple-negative breast cancer.
  - TX/CEX is more effective than T/CEF in patients with >3 axillary metastases (data not shown).
  - TX/CEX improves breast cancer-specific survival (data not shown).

Joensuu H et al. *Proc SABCS* 2010;Abstract S4-1.

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Investigator Commentary: Incorporation of Capecitabine into Adjuvant Therapy for Medium- to High-Risk Early BC

The large US Oncology trial evaluated adjuvant AC followed by docetaxel (T) with or without capecitabine (X). If I "cut to the chase," the disease-free and overall survival curves for the two arms appeared superimposable, although there was a suggestion of a survival benefit with AC followed by XT. Additionally, they suggested that patients with a high Ki-67 derived the greatest benefit from the addition of capecitabine, but I'm not confident that this offers an advantage compared to AC → T.

Interview with William J Gradishar, MD, January 4, 2011

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